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# Daytime sleepiness: more than just Obstructive Sleep Apnea (OSA)

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**Key words:** Daytime sleepiness; Obstructive Sleep Apnea (OSA); hypersomnia

**Parole chiave:** Sonnolenza diurna; Apnee Ostruttive del Sonno (OSA); ipersonnia

**Summary**

*Excessive Daytime Sleepiness (EDS) is a common condition with a significant impact on quality of life and general health. A mild form of sleepiness can be associated with reduced reactivity and modest distractibility symptoms, but more severe symptomatic forms are characterized by an overwhelming and uncontrollable need to sleep, causing sudden sleep attacks, amnesia and automatic behaviors. The prevalence in the general population is between 10 and 25%. Furthermore, EDS has been considered a core symptom of obstructive sleep apnea (OSA), as well as being the main symptom of primary hypersomnias such as narcolepsy types 1 and 2, and idiopathic hypersomnia. Moreover, it can be considered secondary to other sleep disorders (Restless Legs Syndrome, Chronic insomnia, Periodic Limb Movements), psychiatric conditions (Depression, Bipolar Disorder) or a consequence of the intake/abuse of drugs and/or substances. An accurate medical history cannot be sufficient for the differential diagnosis, therefore instrumental recordings by means of polysomnography and the Multiple Sleep Latency Test (MSLT) are mandatory for a correct diagnosis and treatment of the underlying cause of EDS.*

**Riassunto**

***«Sonnolenza diurna: più di una semplice Apnea Ostruttiva nel Sonno (OSA)»***. *L'eccessiva sonnolenza diurna (Excessive Daytime Sleepiness, EDS) è una condizione molto comune con un impatto significativo sulla qualità di vita e sulla salute in generale. Una forma lieve di sonnolenza può accompagnarsi ad una minor reattività e sintomi di modesta distraibilità, ma forme sintomatologiche più gravi sono caratterizzate da un travolgente ed incoercibile bisogno di dormire, con conseguenti attacchi improvvisi di sonno, amnesia e comportamenti automatici. La prevalenza nella popolazione generale si attesta tra il 10 e il 25%. L'EDS è considerata un sintomo cardine delle apnee ostruttive del sonno (Obstructive Sleep Apnea, OSA), oltre ad essere il sintomo caratterizzante delle ipersonnie primarie quali narcolessia di tipo 1 e 2, e ipersonnia idiopatica. Infine, può presentarsi come conseguenza di altri disturbi del sonno (ad esempio, Insonnia cronica, Restless Legs Syndrome, Periodic Limb Movements), condizioni psichiatriche (Depressione, Disturbo Bipolare) o secondaria all'assunzione o all'abuso di farmaci e/o sostanze. Effettuare una diagnosi differenziale mediante un'accurata raccolta anamnestica può non essere sufficiente per l'individuazione e il trattamento delle cause sottostanti all'EDS, per cui spesso divengono necessarie valutazioni strumentali specifiche. La polisonnografia notturna è importante per valutare durata, struttura e possibili cause di frammentazione del sonno; il Test delle Latenze Multiple del Sonno (Multiple Sleep Latency Test, MSLT) è utile, invece, per valutare oggettivamente la propensione all'addormentamento diurno.*

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## 1. Introduction

Daytime sleepiness is a physiological state influenced by circadian and homeostatic factors, as well as external factors and individual characteristics (29). Excessive daytime sleepiness (EDS) is a common condition with a significant impact on quality of life and general health. A timely assessment of the EDS severity is fundamental. A mild form of sleepiness may be accompanied by a low reactivity and symptoms of mild distractibility, while more severe symptomatic forms are characterized by an overwhelming and uncontrollable need to sleep, which may lead to sudden sleep attacks, amnesia and automatic behaviors. In the general population, the prevalence of clinically significant EDS is between 10 and 25% (29, 32). An operative characterization of EDS diagnosis is crucial. The "Hypersomnolence Disorder" has been included in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) (4) and is defined as severe daytime sleepiness after more than 7 hours of sleep with at least one of the following symptoms: recurrent periods of sleep or lapses into sleep within the same day, a prolonged main sleep episode of more than 9 hours per day that is nonrestorative, difficulty being fully awake after abrupt awakening. In addition, EDS episodes must occur for more than 3 times a week for at least 3 months, and result in daytime impairment in cognitive, social, occupational, or other important areas of functioning. Although there is not yet a gold standard for the diagnosis of EDS, a rigorous clinical approach that includes both subjective and objective evaluation is required by the DSM-5. First of all, the use of the Epworth Sleepiness Scale (ESS) (18) and the Multiple Sleep Latency Test (MSLT) (12) are recommended. However, the evaluation of patients presenting Hypersomnolence Disorder should start with a comprehensive medical history. At first, it is necessary to investigate the medication history of the subject, such as intake of drugs that may lead to fatigue and sedation, but also medical and/or physiological problems (such as sleep apnea, insomnia, narcolepsy, idiopathic hypersomnia, psychiatric disorder, sleep deprivation) as well as behavioral problems (such as bad sleep hygiene, substance abuse).

## 2. Daytime sleepiness and Obstructive Sleep Apnea (OSA)

EDS is considered a main symptom in OSA patients and it may influence the therapeutic choice (9). Continuous Positive Airway Pressure (CPAP) is an effective treatment for OSA patients (5). Nevertheless, the association between somnolence and OSA is not clear. Moreover, several studies indicate that many OSA patients, including subjects affected by a severe form, do not report EDS (22). Insomnia is another disease often associated with OSA, but this association has been less evaluated than the association with EDS. Krakow et al. (22) reported the presence of significant insomnia symptoms in 50% of patients affected by OSA and further studies confirmed a high comorbidity (39-58%) (26). Other studies have demonstrated that OSA prevalence is higher in insomniacs compared to the general population (2). In the most recent sleep disorders classifications, DSM-5 and the International Classification of Sleep Disorders – 3 (ICSD-3) (3), the diagnostic criteria for insomnia have been modified. An important change is the elimination of the "nonrestorative sleep" criterion. Since non-restorative sleep is a frequently reported complaint in OSA patients, more than difficulty initiating or maintaining sleep (2), with the new diagnostic criteria the prevalence of OSA in insomnia will probably decrease in future studies. How can this relation between insomnia and OSA be explained? Is it possible to hypothesize that insomnia can exacerbate or contribute to OSA development? Can OSA contribute to insomnia development? Are both disorders reciprocally linked in a relation where they increase each other's severity?

For example, hyperarousal has been hypothesized as a typical feature of insomnia (11), and it may lead to a restriction of deep sleep with consequent increased percentage of light non-REM sleep (stages 1 and 2) and an increased susceptibility to apneic events (31). On the other hand, OSA may cause the development of insomnia symptoms in some patients since the presence of repeated pathological breathing-related events with awakenings may cause an overestimation of wakefulness during sleep (27). When dealing with a chronic insomnia patient

that is non-responder to standard pharmacological treatments for insomnia, an OSA should be always suspected: in this case, a CPAP treatment may resolve both insomnia and sleep-related breathing disorder (24).

In subjects with initial insomnia, worry and frustration about not falling asleep may induce the activation of the sympathetic nervous system: repeated associations between environment, desire to fall asleep and this activation may lead to the development of a "conditioned" insomnia. This may be a problem for OSA patients who have to start CPAP therapy: in these subjects, prolonged sleep latency may increase the difficulty to accept CPAP therapy and the patient may fail to adhere to the treatment (34). If insomnia symptoms are secondary to OSA, there is no need to treat insomnia directly; vice versa, if insomnia is the primary condition, its treatment may promote the compliance to CPAP therapy. Since pharmacological treatment with hypnotics may cause a worsening of sleep-related breathing disorder (15), non-pharmacological interventions, like Cognitive Behavioural Treatment for Insomnia (CBT-I), should be considered. CBT-I works on patient skills and beliefs about his/her insomnia and it proceeds with cognitive restructuring of dysfunctional beliefs and maladaptive habits, showing an excellent response rate, with better long term effects than pharmacological treatments (16). In order to evaluate CBT-I efficacy in OSA patients with insomnia future long term trials are needed (13).

From a clinical point of view, an important issue is the possible characterization of the OSA + insomnia and OSA + EDS patients. To this extent, the study of Bjorvatn et al. (10) evaluated 1,115 suspected OSA patients, by means of polysomnography and a validated insomnia questionnaire (28). These authors reported a positive correlation between EDS and OSA severity, whereas a negative correlation between insomnia and OSA severity was found. As reported in previous studies, the authors confirmed that a significant amount of OSA patients, even severe ones, does not show EDS (8, 21).

The link between EDS and OSA is complicated as there are many factors that should be taken into account, such as Body Mass Index (BMI) and the presence of depressive symptoms. A recent Australian study conducted on male subjects aged 40-88 years demonstrated that depressive symptoms are significantly associated to non-diagnosed OSA and EDS (23). Other authors reported that even in elderly OSA patients, where EDS prevalence is not high (14.9%), depression and male gender resulted predictive factors for daytime somnolence (33).

Moreover, it is important to remember that depression is one of the most frequent causes of residual EDS in CPAP treated patients (14). Nocturia, another common symptom in OSA patients, has been reported as a factor correlated to EDS, independently from OSA severity (1).

### 3. Other causes of daytime somnolence

As specified in the introduction there are many causes of daytime somnolence, that specifically may be divided into primary and secondary. The primary EDS disorders are narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia and recurrent hypersomnia. The prevalence and a summary of the characteristics of these conditions are presented in table 1.

Narcolepsy is characterized by uncontrollable sleep attacks and the sudden intrusion of REM sleep in the waking state (3, 25). Even though this is a relatively rare disease, it is also underdiagnosed (6). Moreover, in the identified cases, the time between the onset of symptoms to diagnosis varies from 5 to 15 years. The onset is usually between 15 and 18 years of age, but it can appear at any age. According to the latest diagnostic classification, there are two types of narcolepsy: Type 1 and Type 2. The first is caused by a severe loss of neurons in the hypothalamus that produce two "excitatory" neuropeptides called orexin-A and orexin-B (or hypocretin-1 and hypocretin-2). Regarding narcolepsy Type 2, the real cause has not been identified yet. On a clinical level the two types of narcolepsy are substantially similar, with the exception of cataplexy which is not present in Type 2. Essential for the diagnosis of narcolepsy is the presence of EDS, in the form of short irresistible sleep attacks, repeated during the day: they do not only occur in favorable situations, such as a sedentary and monotonous activity after a big meal, but also when the subject is engaged in an activ-

**Table 1** - Primary causes of hypersomnolence

| Disorder | Prevalence | Clinical Findings |
|---|---|---|
| Narcolepsy Type 1 | 25-50 per 100.000 | • Hypersomnolence<br>• Cataplexy<br>• Hypnagogic or hypnopompic hallucinations<br>• Sleep paralysis<br>• Dreams during short naps |
| Narcolepsy Type 2 | 20.5 per 100.000 | • Hypersomnolence<br>• Absence of cataplexy<br>• Sleep paralysis and other features of narcolepsy type 1 may be present but less frequent |
| Idiopathic hypersomnia | According to ICSD-3 prevalence and incidence of this disorder are not known | • Hypersomnolence<br>• Unrefreshing naps<br>• Sleep inertia |
| Recurrent hypersomnia | 0.2-1.0 per 100.000 | • Recurrent episodes of several days with severe hypersomnolence<br>• Derealization<br>• Hyperphagia<br>• Hypersexuality<br>• Normal sleep and behavior between episodes |

ity. Unlike other situations in which EDS is present, such as OSA or sleep deprivation, in narcolepsy a 10-to-15-minute nap is restorative. Cataplexy attacks occur in conjunction with a strong emotion and may last from a few seconds to half an hour; they are characterized by a sudden decrease or loss of muscle tone, either total (with fall of the patient), or partial (for example, atonia of the face and neck muscles). In the latter case, the subject is unable to speak, has diplopia and bows his head forward. Cataplexy attacks are the result of an anomalous intrusion of REM sleep in the waking state; this is the same mechanism that determines the other symptoms present in narcolepsy, such as sleep paralysis and hypnagogic hallucinations. In sleep paralysis, the person is unable to move for a short period of time (from a few seconds to 2 minutes) during the wake-sleep transition, or more often upon waking. Hypnagogic hallucinations are equally short: before falling asleep the subject mainly experiences visual hallucinations (dreaming-like episodes). To diagnose narcolepsy, besides clinical aspects, instrumental examination is mandatory. Specifically, a nocturnal polysomnographic recording, followed by MSLT must be performed. The nocturnal polysomnography evaluates the amount of sleep and excludes other causes of daytime hypersomnia, such as OSA. Moreover, MSLT must show an average sleep latency of less than 8 minutes, and the presence of Sleep-Onset REM Period (SOREMP) in at least two tests; a SOREMP in the MSLT may be replaced with a latency of REM sleep less than 15 minutes in the previous polysomnographic recording night. For the diagnosis of narcolepsy type 1, MSLT data can be replaced with a reduced value of hypocretin-1 (<110 pg/mL). Idiopathic hypersomnia is a condition characterized by EDS generally associated with a long duration of nocturnal sleep. Up to now no epidemiological study has been conducted, therefore it is difficult to establish the correct prevalence in the general population. This disorder occurs mainly in adolescents and young adults, and in clinical practice a high degree of familiarity has been observed. It occurs predominantly in chronic form, and in most cases leads to disabling daytime consequences both in occupational and social activi-

ties. Its treatment consists primarily on symptoms management, and pharmacological therapy is frequently prescribed with the same drugs used for the management of EDS in narcolepsy (7). Secondary causes of hypersomnia are heterogeneous. These include: sleep-disordered breathing (OSA, nocturnal hypoventilation, etc.), psychiatric disorders (e.g. Depression), general medical conditions as well as the use/abuse of drugs, insomnia or changes in sleep/wake phase.

Table 2 underlines the importance of making a differential diagnosis throughout a detailed anamnestic evaluation, in order to identify possible secondary cause of EDS. Sometimes, a single question may be enough. For example, if an insufficient-sleep syndrome is suspected, it will be sufficient to ask the subject if during weekends or holidays (when he/she could sleep longer), EDS disappears or decreases. As a matter of fact, sleeping longer than usual does not change the somnolence severity in disorders like OSA or narcolepsy.

Another interesting disorder is Restless Legs syndrome (RLS). Generally, this disease is associated with insomnia, and it is important to note that a certain number of patients may complain of EDS; in this case, an adequate treatment for RLS could

**Table 2** - Secondary causes of hypersomnolence

| Cause | Examples |
|---|---|
| Sleep-disordered breathing | • Obstructive sleep apnea<br>• Upper airway resistance syndrome<br>• Sleep-related hypoventilation<br>• Central sleep apnea |
| Drug induced | • Antihistamines<br>• Anticholinergic<br>• Opiates<br>• Benzodiazepines<br>• Antiepileptics<br>• Drugs (eg, heroin, marijuana, barbiturates)<br>• Antipsychotics |
| Insufficient sleep | • Chronic insomnia<br>• Insufficient sleep syndrome<br>• Restless Legs Syndrome (RLS)<br>• Periodic Limb Movements (PLMS) |
| Circadian rhythm disorders | • Delayed sleep-wake phase<br>• Jet lag<br>• Irregular sleep-wake schedule |
| Psychiatric conditions | • Depression<br>• Bipolar disorder<br>• Somatoform disorders |
| Other general medical conditions | • Traumatic brain injury<br>• Stroke<br>• Anemia<br>• Hypothyroidism<br>• Hepatic encephalopathy<br>• Obesity hypoventilation syndrome (or Pickwick syndrome) |

solve the symptoms and also EDS (19). In addition, patients with RLS usually suffer from sleep fragmentation due to periodic limb movements (PLMs): continuous arousals may determine a bad sleep quality, with subsequent EDS. In this case, an objective evaluation is necessary, through a nocturnal polysomnography (17).

When clinical data do not allow to correctly identify EDS cause, a polysomnography is crucial for a correct diagnosis. On the contrary, objective data seem less important for depression- related EDS. In fact, 1 out of 4 patients with "psychiatric" hypersomnia has an average sleep latency lower than 8 minutes at MLST (30). Moreover, among psychiatric diseases, EDS appears to be most common in bipolar disorder (20); accordingly, it has been demonstrated that hypersomnia occurs more frequently in young patients affected by type 1- bipolar disorder treated with antidepressants (35).

In conclusion, EDS is a common condition in both neurological and psychiatric disorders. Accordingly, it is considered a core symptom of OSA and primary hypersomnias, as well as a secondary complaint of depression and bipolar disorder. In most cases an accurate medical history cannot be sufficient for the differential diagnosis, therefore instrumental recordings by means of polysomnography and MSLT are mandatory for a correct diagnosis and treatment of the underlying cause of EDS.

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